FUJIREBIO® Diagnostics, Inc.

510(k) SUMMARY

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

The assigned 510(k) number is: K093957.

MAR 18 2010

Submitter Information

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Summary preparation date: December 21, 2009

Name of Device

Trade/Proprietary Name: ARCHITECT HE4 Assay
ARCHITECT HE4 Calibrators
ARCHITECT HE4 Controls

Common/Usual Name: Tumor Associated Antigen Immunological Test System
Calibrator
Quality control material (assayed and unassayed).

Regulation Number: 21 CFR 866.6010
21 CFR 862.1150
21 CFR 862.1660

Regulatory Class: Class II

Product Code: OIU
JIT
JJX

Predicate Device

HE4 EIA (K072939)

Device Description

The ARCHITECT HE4 assay is a two-step immunoassay for the quantitative determination of HE4 antigen in human serum using CMIA technology with flexible assay protocols, referred to as Chemiflex.

In the first step, sample and 2H5 anti-HE4 coated paramagnetic microparticles are combined. HE4 antigen present in the sample binds to the anti-HE4 coated microparticles. After washing, 3D8 anti-HE4 acridinium-labeled conjugate is added to create a reaction mixture in the second step. Following another wash cycle, pre-trigger and trigger solutions are added to the reaction mixture. The resulting chemiluminescent reaction is measured as relative light units (RLUs).

A direct relationship exists between the amount of HE4 antigen in the sample and the RLUs detected by the ARCHITECT *i* System optics.

The ARCHITECT HE4 Calibrators are for the calibration of the ARCHITECT *i* System when used for the quantitative determination of HE4 antigen in human serum.

The ARCHITECT HE4 Controls are used for the verification of the accuracy and precision of the ARCHITECT *i* System when used for the quantitative determination of HE4 antigen in human serum.

Intended Use

Reagent Kit
The ARCHITECT HE4 assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of HE4 antigen in human serum.

The assay is to be used as an aid in monitoring recurrence or progressive disease in patients with epithelial ovarian cancer. Serial testing for patient HE4 assay values should be used in conjunction with other clinical methods used for monitoring ovarian cancer.

Calibrator Kit
The ARCHITECT HE4 Calibrators are for the calibration of the ARCHITECT *i* System when used for the quantitative determination of HE4 antigen in human serum.

Control Kit
The ARCHITECT HE4 Controls are used for the verification of the accuracy and precision of the ARCHITECT *i* System when used for the quantitative determination of HE4 antigen in human serum.

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Statement of Substantial Equivalence

The ARCHITECT HE4 assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of HE4 antigen in human serum.

The assay is to be used as an aid in monitoring recurrence or progressive disease in patients with epithelial ovarian cancer. Serial testing for patient HE4 assay values should be used in conjunction with other clinical methods used for monitoring ovarian cancer.

The ARCHITECT HE4 assay is substantially equivalent to the HE4 EIA.. Both of the devices are IVD products and are indicated for the quantitative determination of HE4 antigen in human serum as well as an aid in monitoring recurrence or progressive disease in patients with epithelial ovarian cancer. Serial testing for patient HE4 assay values should be used in conjunction with other clinical methods used for monitoring ovarian cancer.

The regulatory submission will be prepared pursuant to Title 21CFR § 866.6010(b) which states Tumor Markers must comply with the following special controls;

1. Guidance document entitled "Guidance Document for the Submission of Tumor Associated Antigen Premarket Notifications (510(k)s) to FDA".

2. Voluntary assay performance standards issued by the National Committee on Clinical Laboratory Standards (NCCLS).

A comparison of the features of the ARCHITECT HE4 assay and the HE4 EIA are as follows:

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Similarities		
	ARCHITECT HE4 (Proposed Device)	**HE4 EIA (Predicate Device) K072939**
Device Type	*In vitro* diagnostic	*In vitro* diagnostic
Classification	Class II	Class II
CFR section	866.6010	866.6010
Product Code	OIU	OIU
Product Usage	Clinical and Hospital laboratories	Clinical and Hospital laboratories
Intended Use	Quantitative determination of HE4 antigen in human serum. The assay is to be used as an aid in monitoring recurrence or progressive disease in patients with epithelial ovarian cancer. Serial testing for patient HE4 assay values should be used in conjunction with other clinical methods used for monitoring ovarian cancer.	Quantitative determination of HE4 antigen in human serum. The assay is to be used as an aid in monitoring recurrence or progressive disease in patients with epithelial ovarian cancer. Serial testing for patient HE4 assay values should be used in conjunction with other clinical methods used for monitoring ovarian cancer.
Type of Specimen	Human Serum	Human Serum
Specimen Collection Method	Routine Phlebotomy Techniques	Routine Phlebotomy Techniques
Antigen Detected	HE4	HE4
Capture Antibody	Mouse monoclonal (2H5)	Mouse monoclonal (2H5)
Detection Antibody	Mouse monoclonal (3D8)	Mouse monoclonal (3D8)

Differences		
	ARCHITECT HE4 (Proposed Device)	**HE4 EIA (Predicate Device) K072939**
Instrument System	ARCHITECT *i* System	Manual
Principle of Operation	Chemiluminscent Microparticle Immunoassay (CMIA)	Manual Enzymatic Immunoassay (EIA)
Calibrators	6 Levels (0 – 1500 pmol/L)	6 Levels (0 – 900 pM)
Controls	3 Levels (50, 175 and 700 pmol/L) Supplied as separate kit	2 Levels (50 and 400pM) Supplied with Kit
Interpretation of Results	Calibrator Curve	Standard Curve

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Performance Characteristics

Method Comparison:

The ARCHITECT HE4 assay is designed to have a slope of 1.0 ± 0.1 and a correlation coefficient (r) of ≥ 0.90 for serum specimens when compared to a commercially available HE4 EIA. One hundred and ninety-three serum specimens were tested using the ARCHITECT HE4 assay and the HE4 EIA. The data are summarized in the following table.

ARCHITECT HE4 vs. HE4 EIA

Regression Method	n	Slope (95% CI[a])	Intercept (95% CI[a])	Correlation Coefficient
Passing-Bablok[b]	193	0.96 (0.93 to 1.00)	-2.51 (-3.96 to -0.73)	0.97

ARCHITECT HE4 Specimen Range = 20.3 to 918.7 pmol/L
HE4 EIA Specimen Range = 21.9 to 762.3 pmol/L

a CI = Confidence Interval

b A linear regression method with no special assumptions regarding the distribution of the samples and measurement errors.

Precision:

The ARCHITECT HE4 assay is designed to have an imprecision of ≤ 10% total CV. A study was performed based on guidance from the National Committee for Clinical Laboratory standards (NCCLS) document EP5-A2. Testing was conducted at Fujirebio Diagnostics, Inc. using one lot of reagents, calibrators, and controls and at two external sites using two lots of reagents, calibrators, and controls. Three levels of controls and panels were assayed on one instrument per site in replicates of two at two separate times per day for 20 different days. Each instrument used a single calibration curve throughout the study.

Linearity:

The ARCHITECT HE4 assay is designed to be linear across the measurement range of 20.0 to 1500.0 pmol/L. Samples were prepared by mixing serum panels with diluted wash buffer and tested with the ARCHITECT HE4 assay. Based on a study performed by guidance from the NCCLS document EP6-A, the ARCHITECT HE4 assay demonstrated linearity from 20.0 to 1500.0 pmol/L.

Sensitivity (LoB, LoD, LoQ):

The ARCHITECT HE4 assay is designed to have a Limit of Detection (LoD) of ≤ 15 pmol/L and a Limit of Quantitation (LoQ) of ≤ 20 pmol/L. The LoQ is defined as the lowest amount of analyte in a sample that can be accurately quantitated with a total allowable error of ≤ 30%. A study was performed based on guidance from the NCCLS document EP17-A with one zero-level HE4 sample and four low-level HE4 samples.
The samples were tested in a minimum of five replicates once per day for three different days using three reagent lots and two instruments. The Limit of Blank (LoB) was 0.1 pmol/L, the LoD was 0.2 pmol/L, and the LoQ was 0.2 pmol/L.

Specificity:

The tumor markers listed below were evaluated for cross-reactivity with the ARCHITECT HE4 assay. The tumor markers were prepared with ARCHITECT HE4 Calibrator A to achieve the concentrations indicated below. Reactivities greater than 15 pmol/L HE4 (LoD) were not observed.

Tumor Marker	Tumor Marker Concentration
CA 125, CA 15-3, and CA 19-9	up to 3500 U/mL
Carcinoembryonic Antigen (CEA)	up to 1000 µg/L
α-Fetoprotein (AFP)	up to 400 µg/L

Interference:

The ARCHITECT HE4 assay is designed to have an individual recovery of 100 ± 15% and a mean recovery of 100 ± 10% when comparing potential interferents to the control results. The interference studies were performed based on guidance from the Clinical and Laboratory Standards Institute (CLSI) document EP7-A2.

Potentially Interfering Therapeutic Agents and Endogenous Substances

Recovery studies were performed to compare sera containing the following therapeutic agents and endogenous substances at the indicated interferent concentrations with control sera. The data are summarized in the following tables.

Therapeutic Agent	Interferent Concentration	% Recovery Range	Mean % Recovery
Carboplatin	500 µg/mL	99 - 105	102
Cisplatin	165 µg/mL	97 - 98	98
Clotrimazole	0.3 µg/mL	99 - 103	101
Cyclophosphamide	500 µg/mL	101 - 106	104
Dexamethasone	10 µg/mL	97 - 105	101
Doxorubicin	1.16 µg/mL	100 - 105	103
Leucovorin	2.68 µg/mL	102 - 105	104
Melphalan	2.8 µg/mL	98 - 104	101
Methotrexate	45 µg/mL	96 - 100	98
Paclitaxel	3.5 ng/mL	101 - 102	102

Endogenous Substance	Interferent Concentration	% Recovery Range	Mean % Recovery
Bilirubin	20 mg/dL	92 - 103	98
Hemoglobin	500 mg/dL	104 - 113	108
Low Protein	3 g/dL	101 - 107	103
High Protein	12 g/dL	101 - 108	103
Triglycerides	3000 mg/dL	94 - 104	98

Potentially Interfering Clinical Conditions

Six specimens positive for HAMA and six specimens positive for Rheumatoid Factor (RF) were evaluated at the indicated interferent concentration ranges. The data are summarized in the following table.

Clinical Condition	Interferent Concentration Range	% Recovery Range	Mean % Recovery
HAMA	45 - 155 ng/mL	91 - 108	102
RF	21 - 445 IU/mL	98 - 111	103

Monitoring of Disease status in Patients Diagnosed with Epithelial Ovarian Cancer

A study was performed using the ARCHITECT HE4 assay as an aid in monitoring of disease status in epithelial ovarian cancer patients by assessing changes in HE4 levels in serial serum samples from 76 patients compared to changes in disease status. A study involving a total of 430 pairs of observations was undertaken with an average number of 6.7 observations per patient. A positive change in HE4 was defined as an increase in the value that was at least 14% greater than the previous value of the test. This level of change takes into account the analytical variability of the assay. The data are summarized in the following table.

Change in Disease State per Sequential Pair			
HE4 Concentration Change	No Progression	Progression	Total
less than 14%	261	46	307
greater than or equal to 14%	70	53	123
Total	331	99	430

Fifty-four percent (54%) or 53/99 sequential pairs from patients with disease progression demonstrated an HE4 concentration increase of greater than or equal to 14%. Seventy-nine percent (79%) or 261/331 sequential pairs for patients with no disease progression demonstrated an HE4 concentration of less than 14%. The total concordance for this study was seventy-three percent (73%) or 314/430. Clinicians may wish to use other percent changes in HE4 concentration to reflect their preferences in the trade-off between sensitivity and specificity. The following table shows the resulting sensitivities and specificities of the ARCHITECT HE4 assay at various percent changes in ARCHITECT HE4 assay concentrations, together with the positive predictive values (PPV) and negative predictive values (NPV) for the population tested (99 sequential pairs from patients with disease progression and 331 sequential pairs from patients with no progression.)

Percent (%) Change in HE4	Sensitivity [a] (%)	Specificity [b] (%)	PPV [c] (%)	NPV [d] (%)
10	57	75	40	85
14	54	79	43	85
20	48	84	48	85
25	41	87	49	83
50	31	94	60	82
75	21	97	66	80
100	18	98	69	80

a Sensitivity is 100 x (number of sequential pairs with > 14% increase in HE4 concentration from patients with disease progression/total number of sequential pairs from patients with disease progression)
b Specificity is 100 x (number of sequential pairs with < 14% increase in HE4 concentration from patients without disease progression/total number of sequential pairs from patients without disease progression)
c PPV = 100 x (number of sequential pairs with > 14% increase in HE4 concentration from patients with disease progression/total number of sequential pairs > 14% increase in HE4 concentration)
d NPV = 100 x (number of sequential pairs with < 14% increase in HE4 concentration from patients without disease progression/total number of sequential pairs < 14% increase in HE4 concentration)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Mail Center-WO66-G609
Silver Spring, MD 20993-0002

Fujirebio Diagnostics, Inc.
c/o Ms. Stacey Dolan
Regulatory Affairs Specialist
201 Great Valley Parkway
Malvern, PA 19355

MAR 18 2010

Re: k093957
Trade/Device Name: ARCHITECT HE4 assay
Regulation Number: 21 CFR § 866.6010
Regulation Name: Tumor-associated Antigen Immunological Test System
Regulatory Class: Class II
Product Code: OIU, JIT, JJX
Dated: December 22, 2009
Received: December 23, 2009

Dear Ms. Dolan:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into class II (Special Controls), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21

CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820). This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Parts 801 and 809), please contact the Office of *In Vitro* Diagnostic Device Evaluation and Safety at (301) 796-5450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Maria M. Chan

Maria M. Chan, Ph.D.
Director
Division of Immunology and Hematology Devices
Office of *In Vitro* Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

Indications for Use

510(k) Number (if known): k093957

Device Name: ARCHITECT HE4

Indications For Use:

Reagent Kit

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Prescription Use ___X____ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use ___ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

Reena Philip

Division Sign-Off

Office of In Vitro Diagnostic
Device Evaluation and Safety

510K k093957

Indications for Use

510(k) Number (if known): k093957

Device Name: ARCHITECT HE4

Indications for Use:

Calibrator Kit

The ARCHITECT HE4 Calibrators are for the calibration of the ARCHITECT *i* System when used for the quantitative determination of HE4 antigen in human serum.

Prescription Use ___X____ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use ___ (21 CFR 801 Subpart C)

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Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

Leena Philip

Division Sign-Off

Office of In Vitro Diagnostic
Device Evaluation and Safety

510K k093957

Indications for Use

510(k) Number (if known): k093957

Device Name: ARCHITECT HE4

Indications for Use:

Control Kit

The ARCHITECT HE4 Controls are used for the verification of the accuracy and precision of the ARCHITECT *i* System when used for the quantitative determination of HE4 antigen in human serum.

Prescription Use ___X____ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use ___ (21 CFR 801 Subpart C)

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Office of In Vitro Diagnostic Device Evaluation and Safety

510K k093957